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OF THE CHILDREN'S HOSPITAL
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CRYPTOCOCCAL MENINGOENCEPHALITIS

Charlotte C. Campbell, B.S.,* Grace H. Guin, M.D.†

The early diagnosis of cryptococcosis is difficult and would be made with greater frequency if its possibility were kept in mind when considering the list of differential diagnoses in cases of unexplained chronic illness. The portal of infection is still unknown. Both respiratory and genitourinary systems have been implicated. Because the fungus has a predilection for the central nervous system, the patients as a rule die from meningoencephalitis.

CASE REPORT

This 13 year old negro girl had experienced drowsiness for three days before being brought to Children's Hospital on December 17, 1956. She was no longer active, sat most of the time and required assistance when she walked because of weakness of the legs. The day before admission to the hospital she became extremely lethargic and vomited mucoid material twice. There was no accompanying headache or other pain. She had been constipated for ten days. There was no history of injury or trauma.

The patient had been living in Detroit, Michigan from September until shortly before her hospitalization. Before coming to Washington she had been confined to bed for a week with "flu" and her appetite had been poor.

Past history and family history were non-contributory.

At the initial examination, the patient, a well developed, fairly well nourished 13 year old negro girl was in a semi-conscious state. Her rectal temperature was 99.8 degrees, respirations 22 per minute, pulse rate 100 per minute and blood pressure 110/75. Her head was of normal configuration. The right pupil was dilated more than the left, but both reacted to light. Fundoscopic examination showed bilateral papilledema with retinal hemorrhages. There was ptosis of the left eyelid, and a nasal strabismus which had been evident for several years. The ears and nose were normal. The tongue was dry and it deviated to the right when it was protruded. There was marked salivation with thick mucoid saliva; swallowing was poorly coordinated. The lungs were clear to percussion and auscultation. The cardiac rate was 100 per minute; the heart sounds were strong and regular. The abdominal wall was soft; no masses were felt. There was decreased function of the lower extremities which was particularly evident when passive motion was attempted. The patient moved her legs feebly upon deep stimulation, but the limbs were almost completely flaccid when in the passive state. The upper extremities were normal. Kernig's sign was positive; the Babinski reflex was absent; and the deep tendon reflexes were markedly diminished to absent.

Laboratory examination: Blood hemoglobin 14.1 grams per 100 ml., hematocrit 45 per cent, leukocytes 23,800 per cu. mm. with 85 per cent segmented forms, 1 per cent eosinophiles, 7 per cent lymphocytes, 7 per cent monocytes; serum sodium 131 mEq. per liter, potassium 5.0 mEq. per liter, and carbon dioxide combining power

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21.2 mEq. per liter; spinal fluid clear with 92 leukocytes per cu. mm. with 41 per cent lymphocytes, and 59 per cent polymorphonuclears, protein 52 mg. per 100 ml. and sugar 75 mg. per 100 ml.; urine clear, pH 4.5, specific gravity 1.046, albumin 30 mgm. per 100 ml., leukocytes 4 to 5 per high power field, and erythrocytes 3 to 5 per high power field.

X-ray examination of the skull and a right carotid arteriogram revealed no pathological findings.

A posterior fossa craniotomy was performed the day after admission and the biopsied specimen histologically showed only granulation tissue. The following day the child developed respiratory distress. A ventricular tap yielded approximately 7 ml. of fluid under normal pressure. Her condition rapidly deteriorated despite attempts at resuscitation and death occurred three days after her admission to the hospital.

DISCUSSION

Dr. Guin:

On reviewing the autopsy material from this case nothing was found on gross examination which would suggest the diagnosis of fungus infection. Only a small amount of clotted blood was found at the site of surgical exploration. There was no exudate or clouding of the meninges. On histological examination the thymus gland and the abdominal lymph nodes showed areas of granulomatous formation which were suggestive of a sarcoid process. In some of the areas necrosis was present but acid fast stains and stains for fungi yielded negative results. Examination of the liver revealed multiple foci of necrosis and small numbers of lymphocytes. The portal triads also showed infiltration of acute inflammatory cells and lymphocytes. The lungs showed no remarkable findings. The diagnosis was deferred until the material from the brain was available. Histological examination of this organ revealed a marked meningoencephalitis due to cryptococcus.

Prior to craniotomy the spinal fluid was examined for fungi by the India ink method but no capsular material could be identified. Bacterial cultures of the cerebrospinal fluid were negative although the fungi grew on Sabouraud's media.

Cryptococci were found in large numbers on all surfaces of the brain and extended along the entire length of the spinal cord. There was extensive proliferation of reticulum cells and infiltration of lymphocytes. No acute inflammatory changes were present. Both gray and white matter showed cystic areas partially filled with reticulum cells and large numbers of cryptococci. No other organs were found to contain the fungi.

Although routine staining with haematoxylin and eosin frequently reveals the organisms, since the capsular material is composed of polysaccharide, they are better demonstrated with the Gomori silver stain or periodic acid-Schiff stain. More recently Marshall and Silverstein have

infected isolated mice with cryptococcus. After the formation of antibodies in the serum, the serum was treated with certain dyes such as isomers of fluorescein which became tagged to the antibody. The serum containing the tagged antibody was then injected into mice with cryptococcosis. Histological examination of autopsy material stained with methylene blue was examined under ultraviolet light. The tagged antibody appeared as a fluorescent green color coating the capsules of the cryptococci.

A review of the literature reveals that frequently cryptococcosis is found in combination with lymphoma. Drs. Zimmerman and Rappaport at the Armed Forces Institute of Pathology made a study of 60 autopsied cases of lymphoma[1]. Eighteen of those 60 also had a cryptococcus infection. The authors felt that the cryptococcus infection had played a significant role in the illness and death of these patients rather than being present as an incidental finding. Cryptococcosis is probably a relatively rare disease. It appears in both acute and indolent forms. The case presented is an example of the acute form. The portal of entry of the organism still remains unknown. One cannot help but draw the conclusion that the illness from which this girl suffered prior to her central nervous system manifestations was due to the cryptococcus infection. The histological findings in the thymus and lymph nodes consisting of a granulomatous reaction with and without necrosis are similar to findings described in well documented cases of cryptococcosis in the literature.

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Miss Campbell:

Cryptococcus neoformans is one of about ten fungal agents that can produce systemic disease in man, and is probably one of the easiest of the pathogenic fungi to isolate. This does not mean that it is always readily recovered. One ordinarily suspects the disease in meningitis cases, but there are other and diverse symptoms in this extremely protean disease which do not as readily suggest its presence to the clinician. The organism has been found in sputum and blood-tinged exudates, especially from subcutaneous lesions, as well as in spinal fluid. In spite of the high mortality, we have seen cases in which the organisms persist in the spinal fluid for a number of years, the longest on record being eight years. Except for a feeling of lethargy, this particular patient is asymptomatic and returns once a year for a spinal tap; the organism invariably still is demonstrable. This is considered a very unusual situation for, as a rule, it is believed that once the central nervous system is involved the disease is rapidly fatal.

Although *C. neoformans* is to be found in other clinical specimens, we look for it especially in spinal fluid. A direct microscopic examination is made on the sediment following centrifugation at 2500 rpm for five minutes. After discarding the supernatant fluid, a loopful of the sediment is mixed with a drop of saline and a drop of ordinary India ink on a glass slide. A cover slip is placed over the mixture very quickly before it can dry, since India ink preparations must be examined while still wet. The budding or non-budding yeasts (5 to 20 mμ in diameter) surrounded by a wide, gelatinous capsule have an almost translucent appearance against the dark background, and stand out even under low power magnification. The finding of such organisms is usually considered diagnostic; the total procedure requiring little more than five minutes.

The next step is to implant the sediment from the spinal fluid on the usual fungus media. Sabouraud's agar is quite satisfactory for this purpose. Brain-heart infusion agar containing the antibiotics penicillin (20 units per ml.) and streptomycin (40 units per ml.) is frequently used in order to inhibit any bacterial species that might be present, as these rapidly overgrow a culture of *C. neoformans*. An incubation period of 48 to 72 hours is usually required before any growth is apparent on the medium. Sometimes 96 hours elapse before the opaque, cream to tan bacteria-like colonies begin to appear. These enlarge and may become increasingly mucoid, (although some strains lack this characteristic) but never develop aerial hyphae. *C. neoformans* is a yeast in body tissues and remains so regardless of the medium or temperature used for culture *in vitro*. This is in contrast to other pathogenic fungi such as *Histoplasma capsulatum* or *Blastomyces dermatitidis* which are also yeasts in body tissue but grow as filamentous molds when incubated at room temperature. Although *C. neoformans* grows more rapidly and luxuriantly at room temperature, one of the criteria for determining the pathogenicity of a strain is its ability to grow at 37 degrees C.

The colonies are examined microscopically in the same way as the spinal fluid, substituting, of course, a small portion of the yeast growth for the sediment. There is usually considerable variation in the size of the capsule, and occasionally there are no capsules at all in primary isolates, despite the fact that they have already been demonstrated in the body fluid prior to culture. The organism can be made to produce the capsule by daily successive transfer to new Sabouraud's agar slants and incubation at 37 degrees C, or by injection into white mice. However, unless one is aware of this phenomenon one can easily discard this extremely virulent organism as a non-pathogenic yeast. This is probably one of the chief pitfalls in the study of the agent, particularly if one has not previously demonstrated the capsule in the body fluid, *per se*. Recently, however, even this hazard has been reduced. The antifungal antibiotic, actidione (cycloheximide),

rigidly suppresses the growth of *C. neoformans*, as well as that of many saprophytic fungi, the main purpose for which it is usually employed[1]. This drug is much too toxic to be given to human beings, but it can be used to good advantage in the test tube in the identification of this organism. The yeast isolate is transferred simultaneously to a medium that will support the growth of *C. neoformans* and to a medium containing actidione which will inhibit it, for example, Mycosel agar (BBL) or Sabouraud's agar to which the drug has been added. Growth on the medium without this drug and the absence of growth on the medium with actidione is presumptive evidence that the organism is *C. neoformans*. All efforts should then be made to produce capsules in this strain.

Although successive transfer and incubation at 37 degrees C is a satisfactory procedure for this purpose, and the only one possible in many hospital laboratories, a more rapid procedure is the intracerebral or intraperitoneal inoculation of mice with a saline suspension of the suspected strain, or the body fluid from which it was isolated. The infected animals are observed for a period of 5 or 6 days and if death has not meanwhile occurred, one or more of the mice is sacrificed and the spleen and brain examined for encapsulated yeasts. This is accomplished by mixing emulsions of bits of these tissues with India ink and examining as before. Other animals are sacrificed at weekly intervals thereafter. Mice that die, whether in 24 hours or 24 days, are, of course, similarly examined as soon as possible after death. It is often possible to demonstrate the capsule in brain tissues of mice within 24 to 48 hours after intracerebral inoculation, although such rapidity in establishing the diagnosis is not usually critical because of the sombre prognosis.

The mouse inoculation test is used as a second test for pathogenicity. The more virulent strains produce death in 24 to 48 hours after intracerebral inoculation, whereas the less virulent strains may take 4 to 28 days to produce death following injection by the intraperitoneal route. This is a test of considerable importance, for the pathogenic strains of *C. neoformans* do not differ in any other way from the saprophytic strains of this agent that are isolated from fruits, milk and various other sources in nature or, indeed, from those recovered from normal skin. The saprophytic species, so extensively studied by the late Dr. Rhoda Benham at Columbia University, were serologically indistinguishable from the species pathogenic for man, and the capsules produced were just as dominant as the virulent variety[2]. It may be that the immunological typing schema described by Dr. Edward Evans[3, 4], or the fluorescein technic being developed by Drs. Silverstein and Marshall[5], at the Armed Forces Institute of Pathology will eventually provide a means of differentiation. Until then we are dependent on the mouse virulence test and capacity of the organism to grow at 37 degrees C.

Why is the degree of virulence of such importance? Certainly, there is little doubt in the extreme meningeal case that the cryptococcus strain isolated therefrom is a lethal organism. However, there is some evidence that infections caused by this organism are more common than is suspected, and may manifest themselves in a benign form. Persons with subcutaneous lesions caused by *C. neoformans* who yet have no central nervous system involvement have been observed, and the organism has been demonstrated in lung lesions in persons who died from other causes[6, 7]. It is well to remember that little more than ten years ago other fungus diseases were also regarded as rare and invariably fatal. In histoplasmosis and coccidioidomycosis, for example, it is now known that it is the fatal outcome that is unusual among the countless persons who experience primary, pulmonary infections. Moreover, the symptoms in the latter are very similar to those seen in many common viral and bacterial diseases and very different from those that are characteristic of the rare fatal disease caused by *Histoplasma capsulatum* or *Coccidioides immitis*.

C. neoformans is worldwide in its distribution. There is probably no country from which it has not been reported. In our own laboratory where specimens are received from all over the world, *C. neoformans* is isolated more frequently than any of the other systemic fungi except *C. albicans*. In fact, the disease is frequently referred to as "European Blastomycosis", in contrast to our own North American blastomycosis which has been found only in the United States and Canada. The third and perhaps most common name is "Torulosis". Whatever the terminology, the disease is the same and occurs in northern as well as southern climes, thereby removing one more fungus infection from the mislabeled category of "Tropical Disease".

Dr. Chester Emmons at the National Institutes of Health, who has contributed so much to our understanding of fungus diseases, has recently revealed that he has recovered *C. neoformans* from an impressive number of samples of soils contaminated with pigeon excreta[8]. Further observations on this particular source in nature are warranted, especially in relation to detecting a possible early and benign phase of the disease. It is necessary only to recall the association of chicken excreta and primary, pulmonary histoplasmosis to be alerted in this regard[8, 9].

We do not know how soon truly effective drugs will be available for the treatment of fungus disease. One being tested intensely at the present time is Amphotericin B, which has been tried with limited success in human cases of cryptococcosis as well as histoplasmosis and coccidioidomycosis Early discovery and therapy will improve the chances for recovery in the patient with a mycotic infection just as in all other types of infection.

In conclusion, it should be reiterated that *C. neoformans* is not a difficult organism to isolate or to identify. Although all strains are not pathogenic,

beware of the slow capsular production in some strains and constantly remember that spinal fluid is not the only body source from which the organism can be recovered.

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HYPERTHYROIDISM IN CHILDHOOD

Joseph E. Rall, M.D.,* Philip A. Caulfield, M.D.,† William R. Anderson M.D.,‡ John A. Washington, M.D.§

INTRODUCTION

The following case is presented to initiate discussion of the diagnosis and treatment of hyperthyroidism in childhood. In this case medical treatment was followed by surgery because of recurrence after cessation of therapy with propylthiouracil.

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CASE REPORT

B. D., a 10½ year old colored girl was first seen and treated in the Out-Patient Department of Children's Hospital in January 1953 when she was seven years old. Her complaints at that time included a marked weight loss first noted in 1952, "popping" eyes, marked increase in appetite, choking sensation in the throat, and "nervousness". Examination revealed her to have a diffusely enlarged thyroid gland, and she was admitted to the hospital for study.

The past history, except that relating to the present illness was non-contributory. There was no family history of thyroid disease.

At initial hospitalization the child was a well developed, fairly well nourished seven year old colored girl who was noted to have a diffusely enlarged thyroid gland. Her blood pressure was 100/60, and pulse rate 120 per minute. Her vision was 20/20.

Laboratory data included BMR determinations of plus 27, plus 28, and plus 30. Radio-active iodine uptake was reported as 104 per cent. X-rays of her wrists revealed a normal bone age; x-rays of the skull were normal.

Initial therapy consisted of 100 mg. of propylthiouracil administered orally every eight hours. Her symptoms subsided somewhat but the exophthalmus persisted. In January 1954, the dose of propylthiouracil was increased to 150 mg. every eight hours, and in July 1954, to 200 mg. every eight hours. With this latter dose the thyroid gland decreased considerably in size, the pulse rate remained between 80 and 100 per minute, and her symptoms were well controlled.

In February 1956, since she was asymptomatic, gaining weight, and doing well in school, it was decided to discontinue her medication and observe for recurrence of symptoms. She did not keep her clinic appointment, however, and was next seen in October 1956 when she was noted to have marked recurrence of symptoms, a large goiter, and prominent exophthalmus. Treatment was started with 100 mg. of propylthiouracil every eight hours for four days, and then 200 mg. every eight hours; there was considerable improvement.

On November 7, 1956, she was admitted to the hospital for preparation for surgery. At 10 years of age she weighed 69 pounds and was 57½ inches tall. Her blood pressure was 110/55 and pulse rate 120 per minute. Her thyroid gland was diffusely enlarged, symmetrical, and soft. A soft bruit was heard over the right lobe of the gland. No thyroid nodules were palpated; there was marked exophthalmus, and slight tremor of the hands. X-rays of the wrists revealed a bone age of 12 years.

After surgical consultation, Lugol's solution, 15 drops three times daily, was administered for two weeks prior to surgery. The vascularity of the gland decreased and there was marked shrinkage in total size. A subtotal thyroidectomy was performed on November 26, 1956. The post-operative course was uneventful and she was discharged from the hospital on the ninth postoperative day in good condition. Pathological report of the tissue removed at surgery was "hyperplasia of the thyroid gland".

Dr. Washington:

There was never any difficulty in recognizing the nature of this child's illness. Her complaint of a feeling of pressure is an unusual one in childhood, being more common in adults with goiter. The onset at seven years of age was earlier than is usual; the condition appears more often closer to puberty. The response to propylthiouracil was most gratifying once the dose

was pushed up to her requirement (600 mgm. daily), which is twice that ordinarily prescribed for a child. She attended school and led a normal life. At the time the drug was discontinued, after a three year course, the thyroid gland was no longer palpable. It was hoped that her cure would be permanent. Subsequent events proved that this was not so and surgical removal was required.

Dr. Rall:

This child presented no difficulty in differential diagnosis; historically, physically, and by laboratory examination, her findings were classical. The 104 per cent radio-active iodine uptake was probably a technical error since it is almost impossible for anyone to have 100 per cent uptake, and even values above 90 per cent are quite unusual. There is certainly, however, a geographical variation in the normal range of radio-iodine uptake. In New York and three or four other locations in the United States where radio-iodine uptakes are well standardized, the mean uptake in normal individuals is 25 per cent. In Paris, the mean uptake appears to be almost 43 per cent, a value considered to be close to the hyperthyroid range in New York.

The dose of propylthiouracil used was indeed quite large, but merely points out that one should not be unduly cautious about increasing the dose until one gets a response. It may be necessary to give as much as a gram to a gram and a half per day; the necessity for this amount is quite unusual, of course, but large dosage can be given without much worry about complications. One should, however, look for these complications, the major manifestation of which is depression of the leukocyte count.

The decrease in size of the gland to virtually normal is unusual, and certainly this patient, if any, should have had a permanent remission. This case strengthens a position I have maintained for several years, that very few patients will get permanent remissions from propylthiouracil. By permanent remission is meant that propylthiouracil may be discontinued and the patient continue to remain euthyroid for some years. In our experience we consider it fortunate if one-quarter of the patients treated with adequate propylthiouracil therapy for a long period of time remain euthyroid after the drug is stopped. Propylthiouracil does not appear to be a drug that can be given to a patient, cure his disease, and then be discontinued. It must be continued in order to maintain the beneficial effects.

The increase in bone age in this child is of interest. We have found that where hyperthyroidism in children is of long duration or very severe, an increased bone age results. I do not know whether this results in any change in the final height of the affected child. Lerman feels that the mean height eventually achieved by children who had been previously hyperthyroid was above normal. To the contrary, however, if bone maturation (bone age)

is increased, one might expect an eventual shortening of height. This point certainly needs clarification.

In the treatment of hyperthyroidism, the so-called antithyroid drugs may be used. These include propylthiouracil, Methimazole® and a whole variety of others. The antithyroid drugs appear to exert their effect by inhibiting the formation of organic iodine. The exact mechanism by which this occurs is unknown.

Surgical removal of most of the thyroid gland remains one of the mainstays of treatment.

Iodine has been used in the treatment of hyperthyroidism for many years, particularly during the period of preparation for surgery. Its main effect seems to be a partial inhibition of the release of thyroid hormone. Since this mechanism is not completely effective, the length of time during which iodine may be used is relatively short. Before the advent of the antithyroid drugs and radio-active iodine, one preferred to treat patients with hyperthyroidism with only two to four weeks of iodine medication, and then surgically remove the gland before the patients relapsed.

Radio-active iodine may control hyperthyroidism by producing diffuse damage throughout the entire gland.

It is important to remember the individual action of the various drugs when one uses combined therapy. For example, if propylthiouracil is given, the organification of iodine is inhibited and the iodine stores in the thyroid gland become depleted. The gland becomes very avid for iodine presumably because thyroid stimulating hormone increases the total glandular activity. If two weeks before surgical removal is contemplated, propylthiouracil is discontinued and iodine is substituted, the gland then begins to synthesize great quantities of thyroid hormone. If enough iodine has been given to suppress the release of thyroxin, no difficulty is encountered. If the period of iodine medication is unduly prolonged, however, this suppressing effect begins to wear off and the patient then has a huge store of thyroid hormone which will be released from the gland and lead to extreme toxicity.

It is not often appreciated that even the normal thyroid gland has a huge store of thyroid hormone. Hyperthyroid individuals usually, but not always, have somewhat smaller stores. Surgical removal of the thyroid gland in the toxic hyperthyroid patient before proper preparation with antithyroid drugs and iodine is, of course, quite hazardous.

Radio-active iodine in therapeutic amounts usually delivers from six to twelve thousand roentgens to the thyroid gland. In recent years, the question has arisen as to whether this large dose of radiation predisposes the patient to the development of cancer of the thyroid gland at a later date. I know of no reported instances of cancer of the thyroid developing in man after radio-active iodine therapy, even though six to twelve thousand

roentgens directed toward any tissue is potentially carcinogenic. In fact, certain experimental animals given radio-active iodine develop thyroid cancer in significant numbers.

I feel that the administration of radio-active iodine to children is unjustified at the present time since we are not sure of the late effects. Since we do know that surgical removal of the thyroid gland in children usually controls symptoms satisfactorily, our position is that radio-active iodine is best reserved for the patient over 45–50 years old. We never give it to children therapeutically and are even cautious about administering tracer doses, both on the basis of a natural caution and on the basis of three published series of cases of children who had radiation therapy to the thymus or neck and who later developed carcinoma of the thyroid.

Dr. Caulfield:

At Providence Hospital in the District of Columbia there have been a total of 120,040 admissions since 1947; of this group, 370 have been admitted with thyroid disorders. Of the 370 with thyroid disease, there were three children, one with non-toxic goiter, and two with toxic goiter, certainly not a large percentage.

The indications for surgery in children with hyperthyroidism are similar to those of the adult. The first indication is when adequate medical therapy has failed. "Adequate" therapy may mean therapeutic doses of the antithyroid drugs anywhere from one to five years. Many midwestern authors advocate these prolonged trial periods. It is their hope that the onset of puberty will cure the disease. Most authors, however, feel that the incidence of exacerbation is so high that it is better to resort to surgery after a shorter trial period. Surgery is also indicated in the patient who rebels against the necessity for prolonged treatment and observation, who does not cooperate and who voluntarily discontinues medication.

Question: What, if any, are the indications for doing a diagnostic radio-active iodine uptake in a child?

Dr. Rall:

Radiation to the thyroid gland from any amount of radio-active iodine depends on at least four things: the size of the gland, the size of the tracer, the uptake, and how fast the I^{131} is released. The basis for using a radio-active iodine tracer in the child probably depends on whether the question of thyroid disease can be easily resolved by other means. Hypothyroidism in children, for instance, is a serious condition. Determination of the protein-bound iodine usually confirms the diagnosis. However, in the absence of a diagnostic value for this test, if there is a strong clinical suspicion that

a child is hypothyroid, a radio-active iodine tracer is, I think, obligatory. Because the diagnosis of cretinism or myxedema is so important to the further development of the child, the use of the tracer is a calculated risk. On the other hand, in the child who appears only "nervous", in the absence of any other sign of hyperthyroidism, and has a normal blood level of protein-bound iodine, the use of a radio-active iodine tracer becomes a matter of judgment.

If the protein-bound iodine test is performed in a laboratory which has had a great deal of experience in performing it, it is probably the most reliable test in diagnosing hypo or hyperthyroidism. It is, however, a difficult test to perform. A radio-active iodine uptake test is somewhat less technically difficult.

Question: What is the feeling about the treatment of hyperthyroidism in the pregnant woman in relation to possible effects on the baby?

Dr. Rall:

Our feeling is that the best treatment for pregnant women with hyperthyroidism is the cautious use of propylthiouracil to maintain them at the upper level of normal thyroid function. The protein-bound iodine should remain relatively elevated (10–12 mcg. per 100 ml.). We have generally continued the propylthiouracil in as small a dose as possible right up to and through delivery. We do not feel that the last two weeks of pregnancy are much different from the preceding weeks.

It is important to observe the infants of these mothers for respiratory insufficiency resulting from obstruction from congenital goiters immediately after birth.

Question: What should be the disposition of the thyroid gland with one or two nodules?

Dr. Rall:

We are considerably more alarmed about thyroid enlargements in children than we are in adults. It has been our impression that any nodular enlargement of the thyroid gland in the child is dangerous. The incidence of carcinoma in multinodular enlargement of the thyroid in adults is variously estimated to be between one and eight per cent. In children we feel that we must look at any thyroid enlargement with a great deal of suspicion.

REPORT FROM THE LITERATURE

Spontaneous Closure of an Interventricular Septal Defect

Translated from the Italian by: Carmela Torre, M.D.,* Leticia Tina, M.D.†

Comment by: Bernice Wedum, M.D.‡

In 1932, Montanini[1] reported an autopsy performed on a 42 year old woman who died of cancer of the uterine cervix. There had never been any previously described symptoms or signs referable to the heart. No murmur had ever been heard, and signs of cardiac insufficiency were absent. She had had three full-term pregnancies without difficulty and a history of exudative pleurisy three years before death.

Physical examination at the time of her last admission to the hospital showed the lungs to be clear and the heart to be of normal size. The apex beat was felt at the fifth left intercostal space. The cardiac sounds were of good quality and of normal rhythm. Pelvic examination revealed the presence of a uterine tumor.

At post-mortem the pericardium showed extensive adhesions forming a fibrinous film which could easily be removed. Other areas in the epicardium showed an adhesive process which was becoming organized. This was thought to be evidence of a recurrent fibrinous adhesive pericarditis; the heart was described as normal in shape and size. The pulmonary conus appeared slightly thickened but the pulmonary valves were normal. The right auricle was dilated and the endocardium thickened and opaque. Fenestrated membranes which were the remains of the valves of the inferior vena cava (Eustachian) and of the coronary sinus (Thebesian) were present. The anterior and posterior cusps of the tricuspid valve appeared normal. The free edge of the medial leaflet, however, was attached to the wall of the right ventricle; the chordae tendinae to this leaflet were fused to an interventricular septum and were seen as very small folds which had been formed by the endocardium at the site of attachment. The papillary muscles of the medial leaflet were barely formed. The left auricle was normal in appearance; the mitral valve had slightly edematous edges but appeared normal. The endocardium of the left ventricle was thickened and opaque. The aortic valve was normal.

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In the membranous portion of the interventricular septum a round defect was present, measuring 15 mm in diameter. Its borders were regular and smooth and covered by a slightly opaque endocardium. A thin, semi-transparent fibrinous membrane which was part of the parietal surface of the medial cusp of the tricuspid valve was adherent to the defect, thereby closing it. When observed from the left ventricular side, the defect was covered by a small band of tissue which was membranous as it originated from the inferior border of the defect, divided into two very thin fringes as it crossed the defect, and fixed itself at the superior border of the defect; this gave a partially fenestrated appearance to the defect. Examining it against the light one noticed that the muscular part of the septum ended completely at the inferior border of this defect. Through it one could also see the attachment of the chordae tendinae to the inferior surface of the tricuspid valve. It was possible to pass a probe gently from the left to the right ventricle through the inferior edge of the occluding medial cusp which was not completely adherent to the ventricular wall. The myocardium was slightly sclerotic and opaque and there was no ventricular hypertrophy.

The anatomical diagnoses were:

a) Interventricular septal defect (membranous part), compensated by its closure due to adhesion of the medial cusp of the tricuspid, as a result of tricuspid endocarditis, and

b) Fibro-adhesive pericarditis, recurrent.

Additional diagnoses were:

a) Cancer of the uterus

b) Hydronephrosis, mild, left

c) Bilateral hydroureter, and

d) Anemia and degeneration of the viscera

Histological examination showed the following:

The myocardium of both ventricles showed an increase in the interstitial tissue and cloudy swelling of the muscle fibers; no hypertrophy nor chronic inflammation was seen. The pericardium was thickened by layers of fibrin with beginning organization. The endocardium of the lateral walls and of the mitral and tricuspid valves was not remarkable except for slight thickening and irregularity of the connective fibers at the point of insertion of the valves.

Horizontal microscopic sections through the left inferior border of the defect demonstrated a thickened endocardium whose fibers were mixed with fibers arising from the medial tricuspid leaflet. However, one could follow the superficial layer for a few millimeters and see it terminating in a small area where an old inflammatory process was present. The tissue closing the defect was formed exclusively by a thickened tricuspid cusp

containing a moderate amount of muscle fiber. There was histiocytic infiltration and marked distortion of the connective tissue fibers which crossed one another, leading to nodule formation in this area. The superior border of the defect was formed by a very thin membrane lined by endothelial cells extending upward and becoming continuous with the intima of the aorta on the left and the inferior surface of the medial tricuspid cusp on the right. The results of the inflammatory process were evident at the region where the medial tricuspid cusp attached itself to the ventricular wall. Here there was a large area of cicatricial connective tissue containing numerous histiocytes having round or stellate nuclei. The endocardium of the right interatrial surface was thickened and cloudy. The foregoing pathological findings were thought to be evidence of a healed endocarditis, strictly localized to the region of the septum and medial tricuspid leaflet. The author attempts to explain the pathogenic mechanism by which the tricuspid leaflet fused itself with the wall, and the time when this occurred. The histological findings confirmed the fact that the adhesion was a result of an endocarditis strictly localized to the tricuspid leaflet and to the parietal surface of the interventricular septum.

The past history of the patient did not give any indication of a previous pathological process, but rather showed that this woman had three full term pregnancies without any symptoms of cardiac insufficiency. This finding with the absence of a murmur and myocardial hypertrophy together with the absence of chronic, passive congestion of various organs, as found at autopsy, showed that the defect was completely compensated.

The histological findings showed muscle fibers were not present in the two other leaflets. It was assumed, therefore, that only the medial leaflet had partially retained its fetal structure, due to the lack of its valvular function. The lack of development of the papillary muscles and of the chordae tendinae of this leaflet proved that they did not have any part in the cardiac activity. The tricuspid insufficiency due to the absence of one cusp must have been compensated by the other two cusps, so that the myocardium did not need to become hypertrophied (Valvular compensation). All these data are sufficient to conclude that the occlusion of the interventricular opening took place during fetal life. It was believed that in this case there had been a persistence of the interventricular defect as a result of arrested development and a tricuspid valvular endocarditis, limited to one cusp only. Even in the adult endocarditides the localization to only one valvular leaflet is not rare (Supino). The results of the healing process were the definite adhesion of the valvular cusp to the border of the septal defect and the occlusion, and thereby, the compensation, or rather the repair of the latter. In this way the heart was able to function throughout life and undergo episodes of stress without any difficulty.

The adhesive, chronic pericarditis, of undeterminable chronology, was possibly the result of either an inflammation coincident to the endocarditis or of a later episode. The recurrence of the pericarditis could have been related either to the renal pathology (uremic pericarditis), or to infected foci of necrosis from the uterine cancer.

COMMENT

Dr. Wedum:

There are three points of special interest in this communication. It is the first report, as far as we are aware, of spontaneous closure of a ventricular septal defect. Second, it represents an instance of acquired tricuspid insufficiency which either caused little strain on the right auricle or which was compensated for by the anterior and posterior cusps of the tricuspid valves. Finally it documents an additional instance of spontaneous healing of a bacterial endocarditis.

In discussing a review of a large number of ventricular septal defects representing the combined autopsy experiences at Children's Hospital of Washington and Philadelphia recently the question was raised by Dr. Peter Vanace whether the septal cusp of the tricuspid valve could be used to close certain ventricular septal defects where closure with a prosthesis would be technically most difficult. This report demonstrates that such a closure has in fact actually occurred as a natural process at least on one occasion and that further experimental work might demonstrate such a closure to be practically feasible as a surgical procedure.

REFERENCE

1. Montanini, Nello: About a Rare Mechanism of Complete Repair of an Interventricular Septal Defect. Med. ital., **8**: 449, 1932.

DRUG MANAGEMENT OF THE ACUTE HYPERTENSIVE CRISIS IN THE CHILD

Abstract from Discussion at Weekly Clinical Conference

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In discussion of the therapy of the acute hypertensive state in the child, perhaps the first drug to be mentioned is Reserpine. The average effective dose of Reserpine in the adult is 2.5 mg. intramuscularly. A 50 pound child, therefore, would be given 1.0 mg. Although the tranquilizing effect

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of Reserpine is noted in 20 minutes, the antihypertensive effect is not apparent for 3 hours. The average duration of action is nine hours. Obviously, in a convulsing child one cannot rely solely on Reserpine to lower the arterial pressure or to stop the convulsions. In such instances Reserpine must be combined with other drugs which exert their hypotensive action more quickly. Veratrum has proven to be very effective in this regard, and in our experience is more satisfactory than magnesium sulfate.

Unitensen® (Irwin Neisler) seems to be the parenteral Veratrum of choice; this drug shows the least amount of toxicity and the widest therapeutic index. A satisfactory schedule for administering Unitensen® intramuscularly, to a 50 pound child with acute hypertension due to glomerulonephritis would be as follows:

1. Immediate administration of Unitensen®, 0.15 mg. mixed with 1.0 ml. of one per cent Procaine, intramuscularly.
2. Record the blood pressure and pulse every 15 minutes (if the child is ill enough to receive Veratrum he must be watched constantly).
3. Repeat Unitensen®, 0.15 mg. intramuscularly, whenever the blood pressure is above 100/80 mm. Hg: this may be administered as often as every hour, if necessary.
4. If there is no hypotensive effect from 0.15 mg. of purified Veratrum at the end of one hour the dosage is increased to 0.16 mg.; if nausea or vomiting occurs, 25 mg. of Pentobarbital sodium is given intravenously.
5. 1.0 mg. of Reserpine is concurrently administered intramuscularly every 8 to 12 hours.

Obviously, the blood pressure chart and clinical evaluation of the patient will soon inform the physician of the patient's sensitivity to Veratrum. For example, one may find that 0.15 mg. of Veratrum plus 1.0 mg. of Reserpine will maintain the arterial pressure under 100/80 mm. Hg from five to seven hours. Veratrum is then repeated at five to seven hour intervals, as the case demands. The amount and the dosage intervals may vary from patient to patient without any correlation to the initial height of the arterial pressure or the severity of the disease state. The management of each patient therefore must be individualized.

In a convulsing child the intramuscular route of Veratrum should not be utilized since there is usually a delay in action of 20 to 30 minutes. When the arterial pressure must be reduced rapidly as when convulsions are present, the intravenous route for administering Veratrum is utilized.

1. 0.5 ml. of purified Veratrum is mixed with 20 ml. of 5 per cent dextrose in water for intravenous use. With one physician recording the blood pressure every minute and another administering the medication, the Veratrum solution is given intravenously at the rate of one

ml. per minute until the first 20 mm. fall in systolic or 10 mm. reduction in diastolic pressure occurs.

2. The needle is left in place in the vein. No additional Veratrum is given since there will frequently be a precipitous drop in pressure in the subsequent one to two minutes.
3. If after waiting one to two minutes no such reduction occurs, the administration of Veratrum is continued at a rate of one ml. per minute; administration is stopped at the first subsequent sign of hypotension.
4. The needle is then removed and replaced with a 15 gauge needle through which a sterile polyethylene plastic catheter is threaded well into the vein. The 15 gauge needle is then removed and the catheter is taped to the skin of the forearm.
5. A solution of 5 per cent dextrose in water is allowed to drip through the catheter to insure patency. All additional medication is given through this catheter.

After the first hypotensive effect of Veratrum has been witnessed, the catheter being in place, blood pressure recordings are made at 15 minute intervals. Additional Veratrum (half the previous effective dose) is given whenever the blood pressure is 100/80 mm. Hg or above. Once again, a few hours of observation of the blood pressure chart and clinical apparisal of the patient will demonstrate the need for Veratrum at definite intervals, such as every forty minutes or every two hours, the interval between injections becoming longer as the severity of the condition diminishes. If vomiting occurs, 25 mg. of Pentobarbital sodium is administered intravenously. When the interval between Veratrum injections reaches an hour, the intramuscular route of administration may be used.

Although others have apparently been impressed with the efficacy of parenteral Hydralazine (Apresoline®), particularly in combination with Reserpine, we have not been so favorably impressed. Hydralazine is a centrally acting sympatholytic drug; it is not a ganglionic blocking agent. The average adult intramuscular dose is 20 mg.; the average dose for a 50 pound child is 5.0 to 10.0 mg. Following the intramuscular injection there is a delay of action of about 30 minutes. The duration of action is about one hour which is prolonged to one and one-half to two hours when Reserpine is concurrently given. In our experience, Hydralazine is more difficult to administer and has more objectionable side effects than Veratrum.

ADDENDUM

Since preparation of this talk, chlorothiazide (Sharp & Dohme), a new effective non-mercurial inhibitor of tubular reabsorption of sodium and

chloride, has become available. Experience has shown that 250 to 500 mg. of chlorothiazide every 8 to 12 hours administered orally or intravenously greatly enhances the hypotensive effect of Reserpine, Veratrum and hydralazine. So effective is the potentiation of the hypotensive effect of Reserpine that the addition of Veratrum or hydralazine is seldom indicated. The combination of parenteral Reserpine plus chlorothiazide represents the therapy of choice in acute hypertension.

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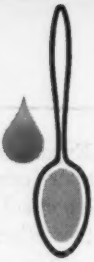

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